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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,936	11/20/2003	Tod R. Smeal	034536-0220	6791

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/716,936	SMEAL ET AL.	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-14 and 18-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6-14, and 18-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/8/08 has been entered.

Claims 1-3, 6-14, and 18-25 are pending.

Claims 1 and 6 have been amended by Applicant.

Claims 1-3, 6-14, and 18-25 are currently under consideration.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6-14, and 18-25 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for the reasons stated in the Office Action of 1/9/08 and for the reasons set-forth below. The claim(s) contains subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also Ex parte Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to methods for monitoring every therapeutic effect of a therapeutic composition on any cancer in a mammal comprising measuring phosphorylation of PAK4 on ser-474 in biopsies before and after administration of a therapeutic composition, wherein a lower level of PAK4 phosphorylation on ser-474 in the biopsy after administration of the therapeutic composition, as compared to the level of PAK4 phosphorylation on ser-474 before administration of the therapeutic composition, indicates that the therapeutic composition has every type of therapeutic effect on cancer in said mammal.

The specification teaches a phosphospecific anti-PAK4 polyclonal antibody, #108, which was raised against a fragment of PAK4 that was phosphorylated on serine-474 (paragraph 52, in particular). The specification further states that phosphospecific antibodies directed against serine-474 detect activated PAK4 (paragraph 4). The specification further states that "The data for the phosphospecific antibody (#108) in colon carcinomas is especially informative (6 out of 6 patients showed marked perinuclear staining in tumor and not distal benign tissue...This result strongly suggests that PAK4 is specifically active in colon tumor cells and inactive in benign colon tissue from the same patient. Staining of phosphorylated PAK4 was also observed in renal cell carcinoma, lung adenocarcinoma, prostatic adenocarcinoma, intraductal breast adenocarcinoma, and ovarian adenocarcinoma" (paragraph 80). The specification further states: "In tumors, strong staining with phosphospecific-PAK4 antibody was identified in colonic adenocarcinomas (while distal benign tissue failed to show phospho-PAK4 staining). On a scale of 0-3, "0" indicates no staining, "1" is indicative of weak staining, "2" indicates moderate staining and "3" indicates strong staining, adenomatous epithelium was faintly to moderately positive, but most normal epithelium showed only staining of "1" for phosphorylated PAK4. Prostatic adenocarcinoma showed moderate staining ("2")" (paragraph 81). The specification further states: "In benign tissues, the most prominent staining for phosphorylated PAK4 was seen in adeipocytes, cardiac myocytes, sebaceous glands, and occasional macrophages. Additional positive cell and tissue types included hair follicles, benign prostatic epithelium, breast epithelium, and urothelium" (paragraph 82). However, the

specification provides no working examples of the claimed invention. The specification only provides general guidelines or prophetic teaching of how changes in PAK phosphorylation levels could be used to monitor an undisclosed effect of a therapeutic composition (paragraph 9, in particular).

This invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology". Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The state of the art is such that if a molecule such as phosphorylated PAK4 is to be used as a surrogate for a particular diseased state, said particular disease state must be identified in some way with phosphorylated PAK4. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. While the teachings of Tockman et al are directed to diagnostics, the teachings of Tockman et al demonstrate the state of the art for predictably using markers to determine any diseased state (such a diseased state of a specific "effect on cancer"). Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the

biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence of a particular change in PAK4 phosphorylation on Ser-474 accompanying a particular effect of a therapeutic composition, one of skill in the art would not be able to predictably determine that said particular change in PAK4 phosphorylation on Ser-474 after administration of a composition gives rise to, or is indicative of, a particular effect without undue experimentation.

The level of unpredictability for using a marker, such as PAK4 phosphorylation on Ser-474, as an indicator of any particular disease state, or therapeutic effect, is quite high. Since neither the specification nor the prior art provide evidence of a universal association between the claimed method and any and every effect of a therapeutic composition, a practitioner wishing to practice the claimed invention would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive.

There has been no demonstration showing that administered compositions that reduce PAK4 phosphorylation on ser-474 result in every or any therapeutic effect. Due to the unpredictability of using a particular biomarker (such as phosphorylation levels of PAK4 on ser-474) as a surrogate for a particular diseased state (such as a particular therapeutic effect), as taught by Tockman et al (see above), one of skill in the art would not predict that the ability of an administered composition to reduce phosphorylation of PAK4 on ser-474 indicates that said composition provides every or any therapeutic effect without such a demonstration.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

In the Reply of 7/8/08, Applicant has submitted a Declaration of Joseph Piraino under 37 C.F.R. 1.132. The Declaration of Joseph Piraino describes experiments wherein small molecule inhibitors of PAK4 reduced PAK4/ser-474 phsophorylation in vivo using various cancer xenograft models. The Declaration of Joseph Piraino further states that reduction in PAK4 corresponds to anti-tumor activity in preclinical mouse xengraft models. Applicant further argues that the Declaration of Joseph Piraino corroberates that at the time of filing Applicant's specification related detailed guidance and provided a level of expectation with respect to the applicability of the disclosed methods across different cancers. Applicant further argues that the skilled person, after reading Applicant's specification, would have: (1) known cancer cells overexpress

phosphorylated PAK4 on ser-474; (2) learned what methods and antibody tools can be used to determine PAK4/ser-474 phosphorylation levels; and (3) have been able to screen candidate compositions to dermine whether any one of them reduces PAK4/ser-474 phosphorylation levels so that detremental consequences of cancer, such as anchorage-independent growth, can be inhibited or slowed by shutting down PAK4/ser-474 phosphorylation.

The amendments to the claims, the Declaration of Joseph Piraino, and the arguments found in the Reply of 7/8/08 have been carefully considered, but are not deemeed persuasive. The Declaration of Joseph Piraino describing experiments wherein small molecule inhibitors of PAK4 reduced PAK4/ser-474 phsophorylation in vivo using various cancer xenograft models is acknowledged. It is noted that the statement that that reduction in PAK4 corresponds to anti-tumor activity in preclinical mouse xengraft models is not supported by demonstrations in the specification or the Declaration.

In regards to the argument that the Declaration of Joseph Piraino corroberates that at the time of filing Applicant's specification related detailed guidance and provided a level of expectation with respect to the applicability of the disclosed methods across different cancers, the specification and the Declaration do not demonstrate enablement of the claimed invention. There has been no demonstration showing that administered compositions that reduce PAK4 phosphorylation on ser-474, such as the small molecule inhbitors of the Declaration, result in every or any therapeutic effect. Due to the unpredictability of using a particular biomarker (such as phosphorylation levels of PAK4

on ser-474) as a surrogate for a particular diseased state (such as a particular therapeutic effect), as taught by Tockman et al (see above), one of skill in the art would not predict that the ability of an administered composition to reduce phosphorylation of PAK4 on ser-474 indicates that said composition provides every or any therapeutic effect without such a demonstration.

The Examiner agrees that after reading Applicant's specification, one of skill in the art would have (1) known some types of cancer cells have high levels of PAK4 with ser-474 phosphorylated, (2) learned what methods and antibody tools can be used to determine PAK4/ser-474 phosphorylation levels, and (3) been able to screen candidate compositions to dermine whether any one of them reduces PAK4/ser-474 phosphorylation levels.

The Examiner disagrees with the arugment that, after reading Applicant's specification, one of skill in the art would have recognized that detremental consequences of cancer can be inhibited or slowed by shutting down PAK4/ser-474 phosphorylation. There has been no demonstration that detremental consequences of cancer are be inhibited or slowed by shutting down PAK4/ser-474 phosphorylation. Again, there has been no demonstration showing that administered compositions that reduce PAK4 phosphorylation on ser-474, such as the small molecule inhbitors of the Declaration, result in every or any therapeutic effect. Due to the unpredictability of using a particular biomarker (such as phosphorylation levels of PAK4 on ser-474) as a surrogate for a particular diseased state (such as a particular therapeutic effect), as taught by Tockman et al (see above), one of skill in the art would not predict that the

ability of an administered composition to reduce phosphorylation of PAK4 on ser-474 indicates that said composition provides every or any therapeutic effect without such a demonstration.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean E Aeder/
Examiner, Art Unit 1642